GENDER-SPECIFIC PRACTICE GUIDELINES for CORONARY ARTERY BYPASS SURGERY

The Society of Thoracic Surgeons Practice Guideline Series
Workforce on Evidence-Based Surgery

STS Practice Guidelines are intended to assist physicians and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. Moreover, these guidelines are subject to change over time, without notice. The ultimate judgment regarding the care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

Gender differences in coronary bypass surgery have been the focus of numerous publications in recent years. Unfortunately these publications have contradictions that leave surgeons with conflicting recommendations for care. To help resolve these inconsistencies, the Society of Thoracic Surgeons Workforce on Evidence-Based Surgery has carried out an objective review of published information in this field. The Workforce recognizes that there are important gender issues associated with referral bias and postoperative support, but the intent of this guideline is to focus specifically on perioperative management. As with all practice guidelines, our goal is to gather the most important information, analyze the information in a logical and unbiased fashion, and make recommendations based solely on the available evidence.

BACKGROUND

Coronary artery bypass graft (CABG) surgery has gained widespread acceptance as an effective treatment option for both men and women. Unfortunately, there is considerable evidence indicating that women carry a higher CABG operative mortality as compared to men [1-10]. The issue is far from settled. Numerous studies [3-10] report either unadjusted or adjusted CABG mortality to be higher in women. Four of these reports [6-9] showed that unadjusted mortality rates were higher in women, but after statistical risk adjustment, the mortality rates were not significantly different. Two of these studies [3,10] demonstrated statistically significant gender differences in both unadjusted and adjusted outcomes. Other reports [11-15] found that unadjusted mortality rates showed no gender difference.

Even with these conflicting studies, one finds considerable evidence to indicate that the female population will generally have a greater operative risk than the male population. 2002 data from The Society of Thoracic Surgeons National Cardiac Surgery Database [16] reveal a CABG operative mortality of 3.54% for women versus a 2.15 % mortality for men. Recognizing that approximately 150,000 women undergo CABG procedures annually in the United States [17], one can show that if the operative mortality of women could be reduced to that of men, the lives of approximately 2,100 women would be saved each year. Certainly all would agree that it is vitally important to search out ways to reduce CABG operative mortality in the female population.

Fortunately, the last decade has produced a surge of public interest and scientific research in women's health , including important gender issues related to CABG . It is now well accepted that there are major differences in the risk profile of men compared to the profile of women undergoing CABG procedures [3,4,7-9,13]. Even when both genders share a common risk factor, the relative impact of a risk factor is often quite different in men as compared to women [3,18,19]. Furthermore, an intervention to medically address the same risk factor may evoke a very different response between the genders [5,6]. Perhaps most importantly, a given postoperative complication appears to have a much more deleterious effect on women compared to men with the same complication [5,6].

An evidence-based analysis of these findings brings into focus several opportunities to provide specific benefit for women undergoing surgical revascularization. For each practice parameter, the workforce has 1.) drawn conclusions supported by the evidence, 2.) provided a statement regarding the ideal clinical practice associated with the practice, and 3.) designated the classification and level of evidence. The criteria used to classify and assign the level of evidence are presented in Appendix A.

1. Use of the Internal Mammary Artery

The use of at least one IMA confers both in-hospital and long-term improvement in CABG mortality [20,21]. In spite of this well-known fact, women receive an internal mammary (IMA) conduit in only 60% to 75% of cases [3,6,8,11-13,22]. This is significantly less than the IMA use in men, thereby creating increased risk in the female population.

The presence of smaller vessels in the female population is often proposed as a reason to avoid IMA use in women, but there is little evidence to substantiate that position. In fact, it has been shown that IMA size is approximately equal in men and women [23], and women are no more likely than men to have native coronary vessels less than 1.5 millimeters in diameter [11,24]. One concludes that the technical challenge in creating an IMA anastomosis should be similar in both the male and female CABG populations.

In most series, there is a higher rate of non-elective CABG in women [3,6,9,12-14]. This should not serve as a deterrent against use of the IMA, since it is usually quite safe to use the IMA when urgent and emergency operations are being performed [25,26].

Perhaps the only time [11] to avoid use of the IMA is when confronted with a soft, friable sternum that predisposes to sternal dehiscence. This should be distinctly uncommon.

The importance of the IMA may be illustrated in a recent study by Aldea and his colleagues [12]. In this study an IMA conduit was used in 91% of women undergoing CABG. They found no gender difference in either crude or adjusted operative mortality. In a 1997 study from Sweden, [8] the IMA was used equally in men and women. The adjusted 30-day mortality rate was approximately equal in these men and women. The 5-year survival rates were also virtually equal in men and women. In these studies one cannot unequivocally attribute the absence of gender mortality differences solely to the high IMA usage in women, but this almost certainly played an important salutary role.

There is no objective reason to use the IMA less frequently in women than men. Current evidence indicates that excess CABG mortality in women can be substantially mitigated with increased use of the IMA, particularly when the left IMA is used to bypass the left anterior descending coronary artery.

Conclusion : Use of the internal mammary artery is underutilized in women undergoing CABG procedures. The internal mammary artery confers a protective effect that is associated with a significant reduction in CABG mortality as compared to surgical revascularization with venous conduits alone.

Ideal Clinical Practice : Whenever it is technically possible, at least one internal mammary artery is used in every CABG procedure to bypass a stenotic coronary artery.
Class I, Level B

2. Management of Hyperglycemia

The association of diabetes with adverse postoperative outcomes is well-known in many surgical specialties, but the sequelae in CABG operations are particularly devastating. There is a clear association with operative mortality [3,6,27,28] as well as mediastinitis and soft tissue wound infections [29-33].

The great majority of studies show that diabetes is 40-50% more common in women than men undergoing CABG, [3,4,7-9,13] Importantly, the adverse clinical impact of diabetes is more pronounced in diabetic women as compared to diabetic men [18].

There is now considerable evidence that diabetic complications and CABG mortality are linked to the degree of perioperative hyperglycemia [18,28,30-34]. Recent studies have shown that the risk of death after CABG is independently related to the degree of perioperative hyperglycemia [28]. Furnary and his colleagues have made a strong argument that the true risk factor is not diabetes per se, but rather *hyperglycemia* with its attendant glycometabolic impairment and relative overutilization of free fatty acids that causes the incremental risk in CABG mortality [31,34]. In addition, hyperglycemia in the first two postoperative days is the single most important predictor of mediastinitis after cardiac surgery [30,31]. In this case the impact of hyperglycemia is directly related to the detrimental effects that high blood glucose levels have on both the immune system and wound healing.

Traditionally, surgeons treating diabetic patients intentionally allowed perioperative blood glucose levels in the 250-300 mg/dl range in order to avoid risking profound hypoglycemia. There is good evidence, however, that both death and infectious complications can be minimized by more strict control of blood glucose. Perioperative continuous intravenous insulin infusions to maintain blood glucose levels well below 200 mg/dl in postoperative diabetic patients have been shown to independently reduce the incidence of mediastinitis by 66% [30,31,33] and the operative mortality by 57% [34]. In one study, the controlled use of continuous insulin infusions resulted in a 50% reduction in the operative mortality of diabetic patients undergoing CABG. It was estimated that the use of perioperative insulin infusions to tightly control blood glucose levels resulted in 21 lives saved for each 1000 patients [34].

The optimal blood glucose level in this clinical context has not been firmly established, but all authorities believe the level should be below 200 mg/dl. It appears that levels in the rage of 100-150 mg/dl are particularly beneficial [30-34].

Since diabetes is more common in women compared to men undergoing CABG, the use of these continuous insulin infusions would predominantly benefit the female CABG population. This should be a particularly important intervention since the sequelae of diabetes are more pronounced in diabetic women as compared to diabetic men [18].

Conclusion : Perioperative blood glucose levels > 150 mg/dl are associated with increased operative morbidity and mortality.

Ideal Clinical Practice : Perioperative blood glucose levels are maintained in the range of 100 - 150 mg/dl.
Class I, Level B

3. Management of Anemia

Even mild anemia in ischemic or unrevascularized patients is associated with an increased risk of postoperative death [35]. During the course of a CABG procedure hematocrit levels are typically lowest during the period of cardiopulmonary bypass (CPB). While some degree of hemodilutional anemia is desirable, it appears that hematocrit levels below 22% during bypass are strongly associated with operative mortality and other postoperative complications [35,36].

It has been shown that women have lower hematocrit levels than men presenting for CABG [12,35-17]. Furthermore, the smaller body size of women results in greater intraoperative hemodilution from the pump prime solution. These factors combine to produce very low hematocrit values in women undergoing cardioplumonary bypass. Recent studies provide firm clinical evidence that women are significantly more likely than men to have profound anemia during CPB [35,36]. In the series reported by Habib and colleagues [36] the average nadir hematocrit in women was 18.7% as compared to 23.1% in men undergoing CABG (p<.001). In this study the operative mortality was 3.3% in women versus 1.9 % in men (p<.001). Both DeFoe [35] and Habib [36] suggest that a major portion of the excess mortality observed in women may well be due to the more profound intraoperative anemia seen in women.

It appears that keeping the nadir hematocrit > 22% during CPB will provide a survival benefit that particularly targets the female population. The nadir value may well be higher than 22%, but at this point, there is no objective evidence to support nadir hematocrit values more than 22%. Approaches to raise the red blood cell concentration may include standard hemoconcentration methods perhaps augmented by modified ultrafiltration. Habib [36] suggests minimizing the pump prime volume by directly modifying the CPB circuitry. Blood transfusions during CPB deserve consideration, but this should be weighed against the possible adverse events associated with transfusions.

Conclusion : Intraoperative hematocrit levels below 22% are associated with an increased incidence of adverse events.

Ideal Clinical Practice : Efforts are made to ensure adequate intraoperative hematocrit levels.
Class IIa, Level B

4. Use of Off-Pump CABG (OPCAB)

There is evidence indicating that women may have better outcomes with OPCAB procedures than with conventional CABG surgery [22,38-40]. In a large multi-institutional study made up entirely of women, Brown [38] found that women undergoing OPCAB had an operative mortality that was 42% lower than a risk-matched group of women undergoing conventional CABG ($p<0.05$). In a retrospective review of 181 women and 232 men, Athanasiou [39] found that female gender was not a predictor of operative mortality in patients undergoing OPCAB. Capdeville [40] retrospectively reviewed results of 187 patients undergoing OPCAB. He found that the operative mortality was more than 3 times higher in women (3.3% for women versus 0.8% for men), but this did not reach statistical significance ($p=.25$).

While OPCAB surgery seems to offer some promise, it should be mentioned that patient selection has been suboptimal in all studies. Brown [38] specifically mentions that the on-pump group in his study had a higher severity-of-illness index than the OPCAB group.

It is also important to note that an IMA is more likely to be used in OPCAB patients compared to conventional CABG patients. This is particularly true for female OPCAB patients. In Brown's study [38] the IMA was used more commonly in the OPCAB women as compared to women undergoing conventional CABG (83% versus 76%, $p<.001$). Athanasiou [39] and his colleagues used an IMA in 92% of women and 93% of men, while Capdeville [40] used the IMA in 100% of women and 98% of men. Since use of the IMA is unequivocally associated with an improved operative mortality, it may be that the improved results seen in OPCAB women are related to the increased use of an IMA conduit.

The favorable results in women undergoing OPCAB suggest the possibility that avoidance of cardiopulmonary bypass might have a selective benefit for women. Since there is no major gender difference in outcomes associated with valve surgery, [41] however, it appears unlikely that the pump itself plays a major role.

Conclusion : There is no evidence to firmly establish the superiority of OPCAB over conventional CABG in the female patient.

Ideal Clinical Practice : The indications for OPCAB surgery are the same for women as for men.
Class IIa, Level B

5. Adjustment of anesthetic and sedation medications

Women require more prolonged postoperative ventilation than men [42,42]. This is an important observation, since the amount of time on the ventilator is correlated to a number of serious complications including pneumonia, sternal dehiscence, mediastinitis, and the need for long-term ventilatory support.

In some institutions, the medications used for anesthesia and immediate postoperative sedation are often dosed without regard for body weight, [42] thereby inducing higher pharmacologic concentrations in the smaller female population. This, in turn, may produce over-sedation that could prolong the period of postoperative ventilatory support. Tailored dosing of anesthetic and sedative medications should minimize over-sedation and thereby reduce the problem of prolonged ventilation and its associated complications.

Conclusion : Failure to account for body size when administering anesthetic and sedative drugs may over-medicate smaller patients.

Ideal Clinical Practice : Anesthetic management and sedative utilization during the perioperative period are tailored to body size.
Class IIb, Level C

6. Optimization of thyroxine treatment for women with hypothyroidism

Hypothyroidism is associated with impaired contractility and an enhanced risk for myocardial infarction. Hypothyroid patients undergoing cardiac surgery may have altered peripheral thyroid hormone metabolism that contributes to this impaired myocardial function.

The impact of this altered physiologic state may be magnified in women. Zindrou and colleagues [19] found a CABG mortality rate of 16.7% in women requiring thyroid replacement therapy. An inverse relationship between CABG operative mortality and both levothyroxine dose and free thyroxine concentration was found in women, but not in men. The operative mortality for hypothyroid men did not differ from that of euthyroid men. Perioperative administration of thyroid hormone or 3,5-diiodothyropropionic acid appears to afford considerable cardiac benefit to these patients [44]. Vigilant perioperative therapy to treat the hypothyroid state in women may serve to minimize the extraordinarily high CABG mortality seen in this important subset of patients.

Conclusion : Low intraoperative levels of levothyroxine and free thyroxin are associated with a high CABG mortality in hypothyroid women.

Ideal Clinical Practice : Hypothyroid women undergoing CABG are maintained in a euthyroid state during surgery.
Class IIa, Level C

7. Consideration of preoperative hormone replacement therapy (HRT)

The use of HRT to attain potentially beneficial cardiovascular effects in women is quite controversial, but there is some evidence that it may be associated with a reduction in CABG operative mortality. A Texas Heart Institute study found that female gender without HRT was an independent risk factor for CABG operative mortality [45]. Women who did not receive HRT experienced a 6.7% mortality, while women receiving HRT had a 2.3% mortality ($p<.01$). The mortality was 2.7% for men. Another study [46] found that CABG mortality for women treated with HRT was significantly better than that of women not treated (2.7% versus 7.4%), but HRT was not a significant predictor of mortality when multivariate analysis was carried out.

Importantly, patients in the HRT group received an IMA conduit significantly more often than those not receiving HRT ($p<.003$). One must therefore ask whether the reduced mortality was due to HRT or to the use of an IMA.

It should also be mentioned that in any study of HRT, the ratio of pre-menopasual to post-menopausal patients should be scrutinized.

A decision to use HRT must be weighed against the well-recognized complications [47] that may be associated with HRT. It should be mentioned that the most recent American College of Cardiology / American Heart Association practice guideline for CABG [48] does not recommend hormone replacement for women undergoing CABG. In fact, this guideline recommends that women on HRT have the hormonal therapy discontinued if CABG is undertaken.

Conclusion : HRT is linked to several complications including serious thromboembolic events. Its use in CABG procedures is of questionable value.

Ideal Clinical Practice : HRT is not used for postmenopausal women undergoing CABG.

Class III, Level B

CONCLUSION

Perioperative practice patterns offer several opportunities to improve CABG outcomes, particularly in women. In contrast to other CABG guidelines [48] which cover the field in a broader and more general scope, this guideline focuses specifically on those measures which surgeons can control. The STS does not consider the recommendations in this guideline to constitute the only acceptable approach to patient management. Surgeons are encouraged, however, to give due consideration to the fact that these recommendations are well-accepted measures that have been extensively reviewed and analyzed with firm adherence to an evidence-based approach.

Appendix A

Classification of Recommendations

Class I	Conditions for which there is evidence and/or general agreement that a given procedure is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure.
	II.a. Weight of evidence favors usefulness/efficacy
	II.b. Usefulness/efficacy is less well established by evidence
Class III	Conditions for which there is evidence and/or general agreement that the procedure is not useful/effective.

Level of Evidence

Level A	Data derived from multiple randomized clinical trials
Level B	Data derived from a single randomized trial or from nonrandomized trials
Level C	Consensus expert opinion

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